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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,681	04/14/2008	Fiona A. Harding	GC840-US	1480

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DANISCO US INC.
ATTENTION: LEGAL DEPARTMENT
925 PAGE MILL ROAD
PALO ALTO, CA 94304

EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,681	HARDING, FIONA A.	
	Examiner	Art Unit	
	GAILENE R. GABEL	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 38-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 38-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/27/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence Compliance Notice*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-13 and 38-47, without traverse, filed November 4, 2010 is acknowledged and has been entered. Claims 13-37 and 47 have been cancelled. Claims 1, 4, and 38 have been amended. Accordingly, claims 1-12 and 38-46 are pending and are under examination.

Specification

2. The disclosure is objected to because of the following informalities: Figure 14A and Figure 14B have not been provided with a differential description.

Appropriate correction is required.

Sequence Compliance

3. It is noted that the Drawings in the instant application, specifically Figures 23-29, disclose therein amino acid sequences. The M.P.E.P., Section 2422.02, 37 CFR 1.821(b) requires exclusive conformance, with regard to the manner in which proteins having a specific nucleotide/amino acids are presented and described, with the sequence rules for all applications that include nucleotide sequences that fall within the definitions. When a sequence is presented, regardless of the format or the manner of the presentation of that sequence, the sequence must be included in a Sequence Listing and a sequence identifier ("SEQ ID NO:X") must be used. It does not appear

that the amino acid sequences in Figures 23-29 are accompanied by sequence identifiers that define them. APPLICANT MUST COMPLY WITH THE SEQUENCE RULES WITHIN THE SAME TIME PERIOD AS IS GIVEN FOR RESPONSE TO THIS ACTION, 37 C.F.R. 1.821-25. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

APPLICANT MUST COMPLY WITH THE SEQUENCE RULES WITHIN THE SAME TIME PERIOD AS IS GIVEN FOR RESPONSE TO THIS ACTION, 37 C.F.R. 1.821-25. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-12 and 38-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, preamble, is vague and indefinite in reciting "in operable combinations" because the term "operable" is a subjective term that lacks a comparative basis for defining its metes and bounds.

Claim 1, step a), part i) lacks clear antecedent basis in reciting, "said animal population", i.e. singular, because the preamble appears to recite "animal populations", i.e. plural; hence, it is unclear as to whether Applicant intends, "said animal populations" or "a subpopulation of the animal populations."

Claim 1, step d) is indefinite in reciting, "exposing said peptides to said CD4+ T-cells" because the term "expose" is a subjective term that lacks a comparative basis for defining its metes and bounds. Does Applicant perhaps intend, "contacting" or "combining" so as to form a mixture between the two components?

Claim 1, step e) lacks antecedent basis for the recitation of "the proliferation response." Claim 1, step e) is further indefinite in failing to clearly define how the proliferation response of the CD4+ T-cells is measured and further assessed, much less individually for each individual peptide produced.

Claim 1, step e) is ambiguous in reciting, "assessing the proliferation response of said CD4+ T-cells to each peptide" of the entire protein sequence in relation to step d), because it is unclear how each individual peptide/fragment effect on the CD4+ T-cells can be detected differentially for the entire protein sequence. How is the proliferation response of said CD4+ T-cells assessed for each distinct peptide of the whole protein sequence differentially. Should each of the produced peptides be differentially labeled and distinctly identified? Should there be a specific immunogenic binding interaction

between the CD4+ T-cells and each of the peptides that should be distinguishably identified and defined so as to allow assessment of the recited proliferation response?

Claim 1, step f) lacks antecedent basis for the recitation of "the stimulation index." Claim 1, step f) is further indefinite in failing to clearly define how the stimulation index of the proliferation response is measured and determined.

Claim 1, step f) is also ambiguous in reciting, "determining the stimulation index of said proliferation profile of said CD4+ T-cells to each of said peptide" of the entire protein sequence in relation to step d), because it is unclear how the stimulation index of each individual peptide/fragment can be determined individually and differentially for the entire protein sequence. How is the stimulation index of the proliferation profile of the CD4+ T-cells determined for each distinct peptide of the whole protein sequence differentially. Should each of the produced peptides be differentially labeled and distinctly identified? Should there be a specific immunogenic binding interaction between the CD4+ T-cells and each of the peptides that should be distinguishably identified and defined so as to allow determination of the recited stimulation index?

Claim 1, step g) lacks clear antecedent basis in reciting, "at least one additional individual" because it is unclear how the "at least one additional individual" structurally and functionally relates to the "individual" in step a), part i) and the "animal populations" in the preamble. Should the "individual" in step a), part i) and the "at least one additional individual" belong to a "same population" of the animal populations? The same analogous comments and problems apply to the recitation of "multiple individuals" Please clarify.

Claim 1, step h) lacks clear antecedent basis in reciting, "multiple individuals." The same analogous comments and problems related to the "individual" in step a), part i), the "animal populations" in the preamble, and the "at least one additional individual" in claim 1, step g), apply to the recitation of "multiple individuals" in the instant claim. Please clarify.

Claim 1, step (i) is vague and indefinite in reciting, "validation assay comprising determining proliferation of unfractionated peripheral blood mononuclear cells (PBMCs) in response to the whole protein sequence of interest" because it is unclear what essential structural and functional cooperative relationships exist between the instant PBMCs, i.e. which encompasses all mononuclear cells including all WBCs, and the [fractionated] monocytes, dendritic cells, and CD4+ T-cells recited in the claim so as to perform a validation assay. Accordingly, claim 1, step (i) also appears to be incomplete in failing to recite method steps which define how the instant "validation assay" in step (i) is performed in relation to the method steps recited in claim 1.

Claim 2 is ambiguous in reciting, "a stimulation index of at least about 1.5 is ... positive" because it is unclear what Applicant intends in such a recitation. Does Applicant intend, "positive immune response" or "positive proliferation response?"

Claim 4 lacks antecedent basis in reciting "the structure values." Additionally, it is unclear what essential structural and functional cooperative relationships exist between "the structural values [of the responses]" and the recited components in claim 1 from which claim 4 ultimately depends.

Claim 38, preamble, is vague and indefinite in reciting "in operable order" because the term "operable" is a subjective term that lacks a comparative basis for defining its metes and bounds.

Claim 38, step e) is indefinite in failing to clearly define how proliferation of the CD4+ T-cells is measured so as to determine a response, much less individually for each individual peptide in the set of peptides.

Claim 38, step e) is ambiguous in reciting, "measuring proliferation of said T-cells in step d) to determine the responses to each peptide in the set of peptides" in relation to step d), because it is unclear how each individual peptide effect on the CD4+ T-cells can be measured differentially for the set of peptides. How is the proliferation of said CD4+ T-cells measured for each distinct peptide of the test protein differentially. Should each of the prepared peptides be differentially labeled and distinctly identified? Should there be a specific immunogenic binding interaction between the CD4+ T-cells and each of the peptides that should be distinguishably identified and defined so as to allow measurement of proliferation and determination of response to each peptide?

Claim 38, step h) lacks antecedent basis in reciting "the structure value of said compiled responses." Additionally, it is unclear what essential structural and functional cooperative relationships exist between "the structural value [of the compiled responses]" and the other recited components in the instant claim.

Claim 38, step i) lacks antecedent basis in reciting "the level of exposure." How does "the level of exposure" relate structurally and functionally to the components recited in step h) of claim 38?

Claim 38 is objected to in having two occurrences of "step (i)."

Claim 38, step (i) in its second occurrence, is vague and indefinite in reciting, "proliferation of unfractionated PBMCs" because it is unclear what essential structural and functional cooperative relationships exist between the instant PBMCs and the monocytes, dendritic cells, and CD4+ T-cells recited in the claim so as to perform a validation assay.

Claim 39 lacks antecedent basis in reciting "said pepsets."

Claim 43 lacks antecedent basis in reciting "the exposure level." How does "the level of exposure" relate structurally and functionally to the components recited in step h) of claim 38?

Claim 46 lacks antecedent basis in reciting "the background percent response" and "the structure values." How do "the background percent response" and "the structure values" relate structurally and functionally to the components recited in claim 38? What is encompassed in the recitation of "the background percent response" and "the structure values."

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims

are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-12 and 38-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-37 of U.S. Patent No. 7,879,571 in view of Harding (CD4+ T-cell Epitope Identification: Applications to Allergy, Clin. Exp. Allergy 33: 557-565 (2003)). Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions recite a method of assessing and ranking immune response profiles in human populations by

combining differentiated monocytic cells or dendritic cells and CD4+ T-cells from a human individual or a group of human individuals belonging to the same population with fragmented set of peptides spanning a whole full length protein having a known amino acid sequence, then measuring the proliferation response of the CD4+ T-cells to each peptide; determining the stimulation index of the CD4+ T-cells to each of the peptides; repeating the same method in duplicate, compiling all the results, and then determining a structure value of the responses observed for the individuals within the same population so as to compare the results of multiple individuals within the same population.

U.S. Patent No. 7,879,571 differs from the instant invention in failing to recite further performing a validation assay comprising determining proliferation of unfractionated peripheral blood mononuclear cells (PBMCs) in response to the whole protein sequence.

Harding teaches in vitro methods for epitope identification and validation. According to Harding, the validation of predicted CD4+ T-cell epitope peptides involves using cells from sensitized donors to determine as to whether a previously exposed donor has mounted a response to that particular peptide. Specifically, Harding teaches performing validation assays by obtaining and culturing unfractionated PBMCs from sensitized human donors in vitro with the peptides or fragments spanning the whole protein, then determining the proliferation of the unfractionated PBMCs in response to the whole protein sequence of interest (p. 560, col. 1, 2nd full ¶).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to perform a validation assay using unfractionated PBMCs as taught by Harding into the method of assessing and ranking immune response profiles as taught in U.S. Patent No. 7,879,571 because Harding taught that unfractionated PBMCs from human sensitized donors cultured in vitro can be used in validation of immunogenicity methods to identify epitopes in proteins that are capable of stimulating a proliferation response in CD4+ T-cells; hence, applicable for the method of assessing and ranking immune response profiles as taught in U.S. Patent No. 7,879,571.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-12 and 38-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stickler et al. (An In Vitro Human Cell-Based Assay to Rank the Relative Immunogenicity of Proteins, 2004, Toxicological Sciences 77 (2): 280-289 (Advanced Access Publication December 22, 2003)) in view of Harding (CD4+ T-cell Epitope Identification: Applications to Allergy, Clin. Exp. Allergy 33: 557-565 (2003)).

Stickler et al. disclose a method for determining or assessing immune response profiles of a human individual or a group of human individuals belonging to a test population (i.e. donor sample group, pools, multiple individuals) against a whole test

protein or a plurality of whole test proteins (Abstract; p. 281, col. 2, 1st ¶; p. 286, col. 1, 1st full ¶ bridging to p. 287, col. 2). Stickler et al. teach obtaining monocytic cells and CD4+ T-cells from individual(s) and then obtaining a test protein or a plurality of test proteins having known protein sequences. The method is essentially repeated in duplicate for the protein(s) listed having known protein sequences so as to obtain comparative immune profiles for the individual(s). The protein(s) is fragmented into a set of peptides, each peptide having 15 amino acids in length, overlapping by about three amino acids and spanning or encompassing the entire test protein sequence (p. 281, col. 2, 2nd, 3rd, 6th and full ¶; Figure 3; Figure 5). The protein(s) having known protein sequences include enzymes (protease, α-amylase, alcalase), soluble receptors (erythropoietin, thrombopoietin), structural proteins (β2-microglobulin), hormones, and binding proteins (p. 281, col. 2, 3rd full ¶). Thereafter, Stickler et al. teach differentiating the monocytic cells into dendritic cells (DCs); hence, differentiated DCs (p. 281, col. 2, 4th and 5th full ¶). Stickler et al. teach combining each peptide of the set of peptides to the differentiated DCs and CD4+ T-cells from the individual(s) in 96-multiwell format and then measuring and assessing the proliferation response of the CD4+ T-cells to each of the peptides by scintillation counting and determining the average count per minute (CPM) value for all the peptides for each set of duplicate (i.e. repeated) wells. Controls are also ran and assayed for individual / donor samples in the absence of peptide (p. 281, col. 2, 6th full ¶ bridging to p. 282, col. 1, 2nd full ¶). Stickler et al. further teach determining the stimulation index (SI) of the measured proliferation profile responses by dividing the average CPM values for each peptide by the average value of the control.

An SI value of at least about 1.5 (i.e. equal to or larger that 2.95) is recorded as positive proliferation response. The responses of the CD4+ T-cells from the individual(s) to each individual peptide of the full length protein are compiled (Abstract; p. 282, col. 1, 2nd full ¶). Stickler et al. teach obtaining and determining a structure value of responses observed for the individual(s) within the group which represents total variation distance between the empirical frequencies and the uniform distribution. The structure value is determined using the formula set forth in page 282, third full paragraph (Abstract; p. 282, col. 1, 3rd full ¶). The background percent response and structure values of each peptide for the test proteins are measured, categorized, and ranked (p. 282, col. 2, 2nd full ¶). The structure value of four proteins (respiratory allergens), namely, amylase (0.81), alcalase (0.72), B. lentus subtilisin (0.64), and BPN' Y217L (0.52) are used to rank the relative immunogenicity of the proteins. A lower structure value, 0.52, indicates that the BPN' Y217L protein is less immunogenic or hypoimmunogenic. A higher structure value, 0.81, indicates that the amylase protein is more immunogenic or hyperimmunogenic (p. 284, col. 1, 3rd full ¶ bridging to p. 285, col. 1; Table 1). Each one of the proteins may be modified to produce a modified protein having a modified epitope (i.e. amino acid sequence) by substitution of an at least one amino acid; thus, producing a variant protein of interest (epitope modified variants) (p. 285, col. 2, last full ¶ bridging to p. 286, col. 1; Figure 8).

Stickler et al. differ from the instant invention in failing to teach further performing a validation assay comprising determining proliferation of unfractionated PBMCs in response to the whole protein sequence.

Harding teaches in vitro methods for epitope identification and validation. According to Harding, the validation of predicted CD4+ T-cell epitope peptides involves using cells from sensitized donors to determine as to whether a previously exposed donor has mounted a response to that particular peptide. Specifically, Harding teaches performing validation assays by obtaining and culturing unfractionated PBMCs from sensitized human donors in vitro with the peptides or fragments spanning the whole protein, then determining the proliferation of the unfractionated PBMCs in response to the whole protein sequence of interest (p. 560, col. 1, 2nd full ¶).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to perform a validation assay using unfractionated PBMCs as taught by Harding into the method of assessing and ranking immune response profiles as taught by Stickler because Harding taught that unfractionated PBMCs from human sensitized donors cultured in vitro can be used in validation of immunogenicity methods to identify epitopes in proteins that are capable of stimulating a proliferation response in CD4+ T-cells; hence, applicable for the method of assessing and ranking immune response profiles as taught by Stickler.

Remarks

7. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Stickler et al. (Human population-based identification of CD4+ T-cell peptide epitope determinants, Journal of Immunological Methods 281: 95-108 (2003)) teach a

human cell-based method to identify functional CD4+ T-cell epitopes in any protein, wherein proteins are tested as synthetic 15-mer peptides offset by three amino acids, and percent proliferation profile responses within a large donor population are obtained for each of the peptides.

Stickler et al. (CD4+ T-cell Epitope Determination Using Unexposed Human Donor Peripheral Blood Mononuclear Cells, Journal of Immunotherapy 23 (6): 654-660 (2000)) teach a dendritic cell-based assay that identifies CD4+ T-cell epitopes in novel proteins using unexposed donors. Predicted T-cell epitopes in the protein of interest are confirmed using cells from verified exposed donors.

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAILENE R. GABEL whose telephone number is (571)272-0820. The examiner can normally be reached on Monday, Tuesday, Thursday, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

April 14, 2011